



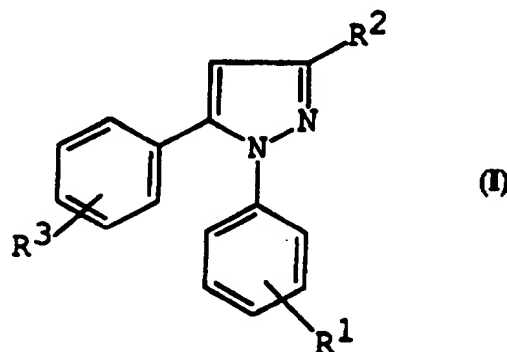
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: 1,3,5-TRISUBSTITUTED PYRAZOLES FOR TREATMENT OF INFLAMMATION

## (57) Abstract

A compound of the formula (I) wherein R<sup>1</sup> is hydroxyethyl, 1-hydroxy-1-methylethyl, hydrogen, halogen, nitro, or cyano, R<sup>2</sup> is chloro, cyano, or lower alkyl optionally substituted with halogen, and R<sup>3</sup> is lower alkylthio, lower alkylsulfinyl, or lower alkylsulfonyl, provided that when R<sup>1</sup> is hydrogen, halogen, nitro, or cyano, then R<sup>2</sup> is chloro, and a pharmaceutically acceptable salt thereof, processes for their preparation and pharmaceutical compositions.



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## DESCRIPTION

## 1,3,5-TRISUBSTITUTED PYRAZOLES FOR TREATMENT OF INFLAMMATION

5           This invention relates to novel pyrazole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

10           More particularly, it relates to novel pyrazole compounds, which have pharmaceutical activity such as inhibiting activity of cyclooxygenase-2 (hereinafter described as COX-II), to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

15           Accordingly, one object of this invention is to provide the novel pyrazole compounds, which have an inhibiting activity of COX-II.

          Another object of this invention is to provide a process for production of the pyrazole compounds.

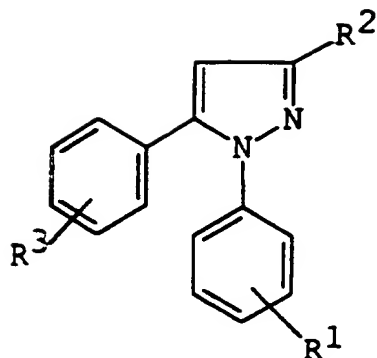
20           A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the pyrazole compounds.

25           Still further object of this invention is to provide a use of the pyrazole compounds for manufacturing a medicament for treating or preventing various diseases.

          Some pyrazole derivatives having antiinflammatory and analgesic activities have been known as described, for example, in Canadian Patent 1 130 808, and EP Patent Publication Nos. 248 594, 272 704, 293 220, 418 845 and  
30           554 829, and WO Patent Publication Nos. 95/15315, 95/15316, 95/15317 and 95/15318.

          The object pyrazole derivatives of this invention are new and can be represented by the following general formula  
35           [I].

2



[I]

15 wherein R<sup>1</sup> is hydroxyethyl, 1-hydroxy-1-methylethyl,  
hydrogen, halogen, nitro, or cyano,  
R<sup>2</sup> is chloro, cyano, or lower alkyl optionally  
substituted with halogen, and  
R<sup>3</sup> is lower alkylthio, lower alkylsulfinyl, or  
20 lower alkylsulfonyl,  
provided that when R<sup>1</sup> is hydrogen, halogen, nitro, or  
cyano,  
then R<sup>2</sup> is chloro,  
and a pharmaceutically acceptable salt thereof.

25

The object compound [I] or a salt thereof can be  
prepared by the following processes.

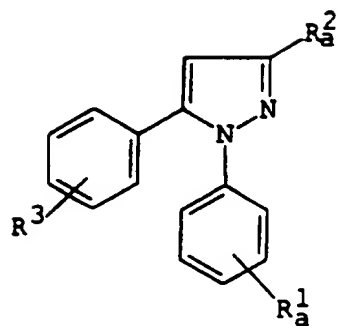
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Process 1

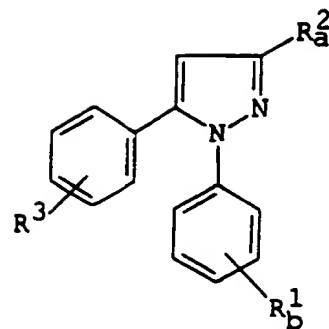
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10



[II]  
or a salt thereof

reduction



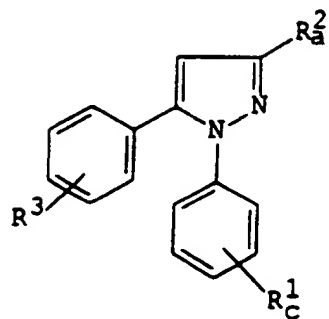
[Ia]  
or a salt thereof

15

Process 2

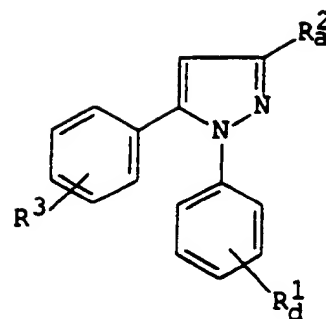
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25



[III]  
or its reactive derivative  
at the carboxy group,  
or a salt thereof

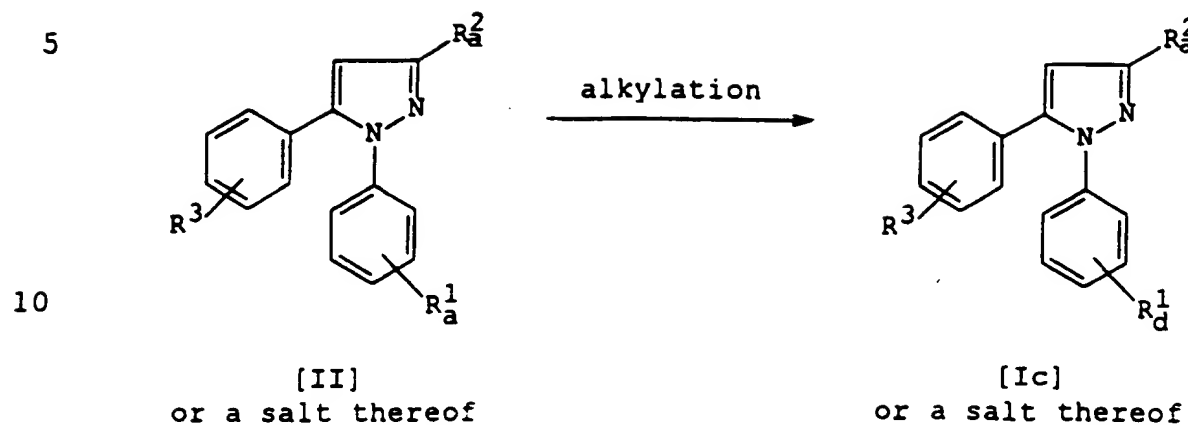
alkylation



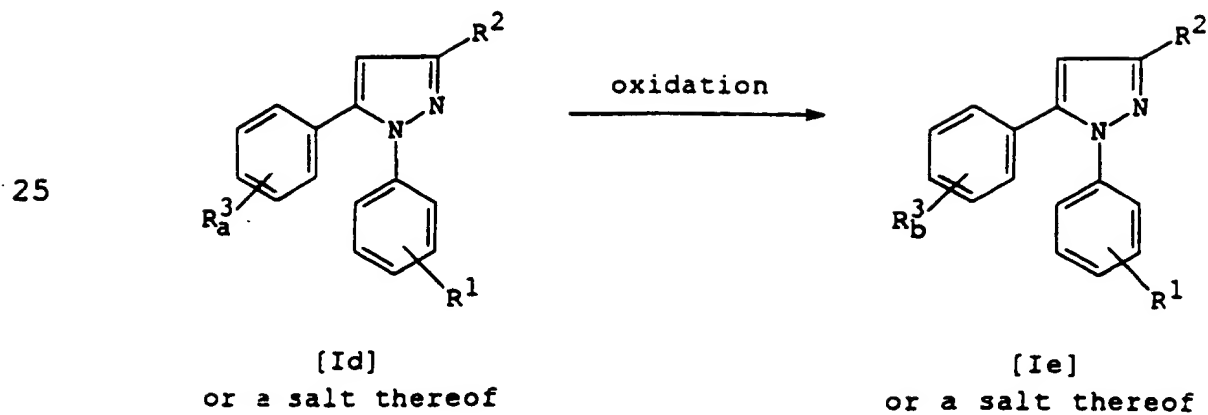
[Ib]  
or a salt thereof

30

35

Process 3

15

Process 4

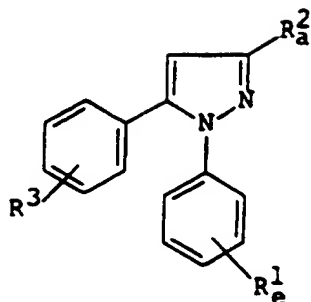
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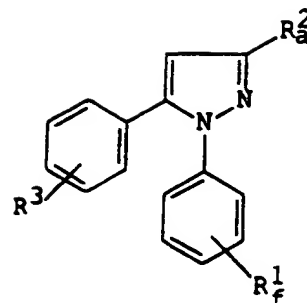
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Process 5

5



reduction



10

[IV]

or its reactive derivative  
at the carboxy group,  
or a salt thereof

[If]

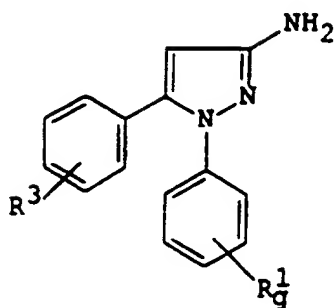
or a salt thereof

15

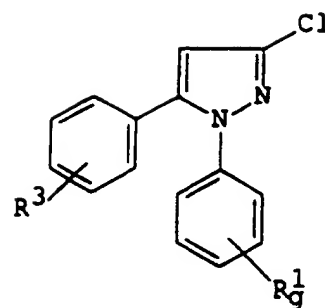
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Process 6

25



chlorination



30

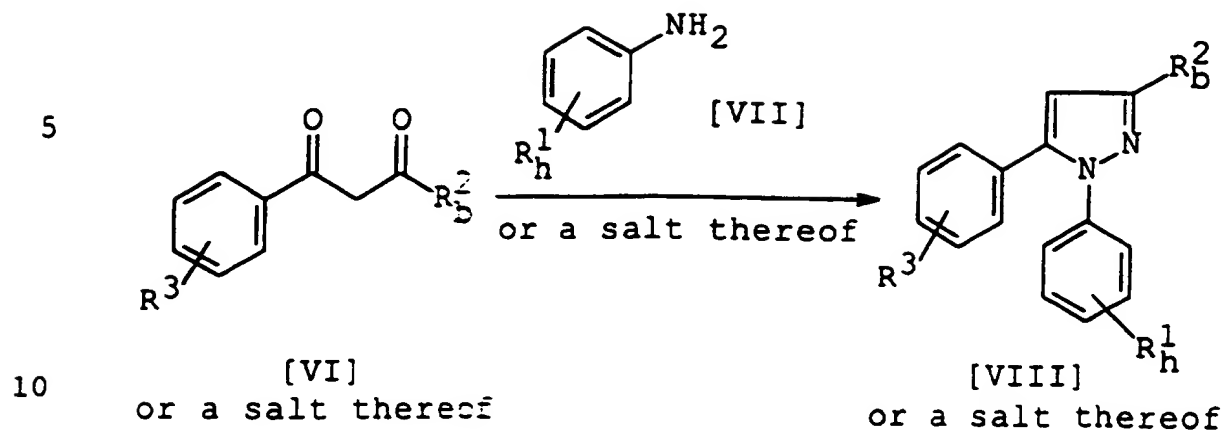
[V]

or a salt thereof

[Ig]

or a salt thereof

35

Referential Process

wherein  $R^1$ ,  $R^2$  and  $R^3$  are each as defined above,

$R_a^1$  is acetyl,

$R_b^1$  is 1-hydroxyethyl,

$R_c^1$  is carboxy,

$R_d^1$  is 1-hydroxy-1-methylethyl,

$R_e^1$  is carboxymethyl,

$R_f^1$  is 2-hydroxyethyl,

$R_g^1$  is hydrogen, halogen, nitro or cyano,

$R_h^1$  is lower alkanoyl, hydroxyethyl, 1-hydroxy-1-methylethyl, hydrogen, halogen, nitro, or cyano,

$R_a^2$  is cyano or lower alkyl optionally substituted with halogen,

$R_b^2$  is halogen, cyano, or lower alkyl optionally substituted with halogen,

$R_a^3$  is lower alkylthio, and

$R_b^3$  is lower alkylsulfinyl or lower alkylsulfonyl.

In the above and subsequent description of the present specification, suitable examples of the various definitions



to be included within the scope of the invention are explained in detail in the following.

5 The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "hydroxyethyl" is intended to mean 1-hydroxyethyl or 2-hydroxyethyl.

10 Suitable "lower alkyl" and lower alkyl moiety in the terms "lower alkylthio", "lower alkylsulfinyl" and "lower alkylsulfonyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which preferable one is methyl.

15 Suitable "lower alkylthio" may be methylthio, ethylthio, propylthio, and the like, in which preferable one is methylthio.

Suitable "lower alkylsulfinyl" may be methylsulfinyl, ethylsulfinyl, propylsulfinyl, and the like, in which preferable one is methylsulfinyl.

20 Suitable "lower alkylsulfonyl" may be methylsulfonyl, ethylsulfonyl, propylsulfonyl, and the like, in which preferable one is methylsulfonyl.

Suitable "halogen" may be fluoro, chloro, bromo and iodo.

25 Suitable "lower alkyl substituted with halogen" may be difluoromethyl, trifluoromethyl, and the like.

Suitable "lower alkanoyl" may be formyl, acetyl, propionyl, butyryl, isobutyryl, and the like.

30 Suitable pharmaceutically acceptable salts of the compounds [I] are conventional non-toxic salts and include an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic  
35 acid addition salt [e.g. hydrochloride, hydrobromide,

sulfate, phosphate, etc.], a salt with an amino acid [e.g. aspartic acid salt, glutamic acid salt, etc.], and the like.

5 The compounds [I] and pharmaceutically acceptable salt according to present invention may contain one or more asymmetric centers, and thus they can exist as enantiomers or diastereoisomers, and the invention includes both mixtures and separate individual isomers.

10 The compound [I] and pharmaceutically acceptable salt thereof according to the present invention can be in the form of a solvate, which was included within the scope of the present invention. The solvate preferably includes a hydrate, an ethanolate, and so on.

15 Also included in the scope of invention are radiolabelled derivatives of compounds [I] which are suitable for biological studies.

#### Process 1

20 The compound [Ia] or a salt thereof can be prepared by reacting a compound [II] or a salt thereof with a reducing agent.

Suitable reducing agent may be diborane, sodium borohydride, lithium aluminum hydride, and the like.

25 The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

30

#### Process 2

The compound [Ib] or a salt thereof can be prepared by reacting a compound [III] or its reactive derivative at the carboxy group, or a salt thereof with alkylating reagent.

35 Suitable reactive derivative at the carboxy group of

the compound [III] may include an ester, an acid anhydride and the like. The suitable examples of the reactive derivatives may be a symmetrical acid anhydride; a mixed acid anhydride with 1,1'-carbonyl diimidazole or an acid such as aliphatic acid [e.g. acetic acid, pivalic acid, etc.], substituted phosphoric acid [e.g. dialkylphosphoric acid, diphenylphosphoric acid, etc.]; an ester such as lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, hexyl ester, etc.], substituted or unsubstituted ar(lower)alkyl ester [e.g. benzyl ester, p-chlorobenzyl ester, etc.], substituted or unsubstituted aryl ester [e.g. phenyl ester, tolyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, pentachlorophenyl ester, naphthyl ester, etc.], or an ester with N,N-dimethylhydroxylamine, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-6-chloro-1H-benzotriazole, or the like.

Suitable alkylating reagent may be organometallic compound such as alkyl lithium (e.g. methyl lithium, ethyl lithium, etc.), alkyl magnesium halide (e.g. methyl magnesium bromide, ethyl magnesium bromide, etc.) and so on.

The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried under cooling to heating.

### 30 Process 3

The compound [Ic] or a salt thereof can be prepared by reacting a compound [II] or a salt thereof, with alkylating reagent.

This reaction can be carried out in substantially the same manner as that of Process 2, and therefore the

reaction mode and reaction conditions [e.g. reagent solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 2.

5     Process 4

The compound [Ie] or a salt thereof can be prepared by reacting a compound [Id] or a salt thereof with an oxidizing agent.

10     The suitable oxidizing agent may be hydrogen peroxide, cumene hydroperoxide, tert-butyl hydroperoxide, Jones reagent, peracid [e.g. peracetic acid, perbenzoic acid, m-chloroperbenzoic acid, monopersulfate compound (oxone<sup>®</sup>), etc.], chromic acid, potassium permanganate, alkali metal periodate [e.g. sodium periodate, etc.], and  
15     the like.

This reaction is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [e.g. methanol, ethanol,  
20     etc.], a mixture thereof or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 5

25     The compound [If] or a salt thereof can be prepared by reacting a compound [IV] or its reactive derivative at the carboxy group, or a salt thereof with a reducing agent.

Suitable reducing agent may be diborane, sodium borohydride, lithium aluminum hydride, and the like. When  
30     a chiral reducing reagent, such as a combination of borane and (R) or (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine, is used, a chiral compound [If] is obtained.

The reaction is usually carried out in a conventional  
35     solvent such as diethyl ether, tetrahydrofuran, or any

other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

5

#### Process 6

The compound [Ig] or a salt thereof can be prepared by the following methods.

Namely, 1) the compound [V] or a salt thereof is  
10 firstly reacted with a nitrite compound, and then 2) the resulting product is reacted with cuprous chloride.

Suitable nitrite compound may be alkali metal nitrite [e.g. sodium nitrite, potassium nitrite, etc.], alkyl nitrite [e.g. isoamyl nitrate, tert-butyl nitrite, etc.],  
15 and the like.

In the first step, the reaction is preferably carried out in the presence of an acid [e.g. hydrochloric acid sulfuric acid, etc.].

The reaction is usually carried out in a solvent such  
20 as water, tetrahydrofuran, dioxane, acetonitrile, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out under cooling to warming.

25 In the second step, the reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium chloride, etc.] and an inorganic acid [e.g. hydrochloric acid, etc.].

The reaction is usually carried out in a solvent such  
30 as water, tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out warming to heating.

### Referential Process

The compound [VIII] or a salt thereof, which includes some of the compound [I] and the starting compounds usable for its preparation processes, can be prepared from the  
5 compound [VI] or a salt thereof and the compound [VII] or a salt thereof by the following method.

First the compound [VII] can be converted to the corresponding hydrazine derivatives by reacting with metal nitrite (e.g. sodium nitrite, etc.) and reducing agent  
10 (e.g. tin chloride, etc.) under the acidic condition. Then the hydrazine derivatives can be reacted with the compound [VI] to give the compound [VIII].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane,  
15 toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

20 The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as  
25 pulverization, recrystallization, column chromatography, reprecipitation, or the like.

Suitable salts of the compound [Ia] to [Ig], [II], [V], [VI], [VII] and [VIII] may be the same as those exemplified for the compound [I].

30 Suitable salts of the compound [III] and [IV] are an alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], and the like.

35 The object compound [I] or pharmaceutically acceptable

salts thereof possesses inhibiting activity of COX-II and possesses strong antiinflammatory, analgesic, antithrombotic, anti-cancer activities and so on. The object compound [I] and pharmaceutically acceptable salts thereof, therefore, are useful for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals, and more particularly for the treatment and/or prevention of inflammation and pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodosa, rheumatic fever, Sjögren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimer's disease, and the like. Additionally, the object compound [I] or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular

diseases, the diseases caused by hyp rglycemia and hyperlipemia.

In order to illustrate the usefulness of the object  
5 compound [I], the pharmacological test data of the compound [I] are shown in the following.

[A] ANTIINFLAMMATORY ACTIVITY :

10 Effect on adjuvant arthritis in rats :

(i) Test Method :

Ten female Sprague-Dawley rats were used per group.  
15 A dose of 0.5 mg of Mycobacterium tuberculosis (strain M37 BA) suspended in 0.05 ml of liquid paraffin was injected subcutaneously in the right hind paw. The injection of mycobacterial adjuvant produced local inflammatory lesions (primary lesion) and then about 10 days later, secondary  
20 lesions in both the injected and uninjected paws. The volumes of both paws before and on days 23 after the injection was measured as percent inhibition in comparison to vehicle-treated controls. The drug was given orally once a day for 23 consecutive days from day 1 after the  
25 injection.

(ii) Test Results :

| Test compound<br>(Example No.) | Dose<br>(mg/kg) | Inhibition of secondary<br>lesion (uninjected paw) (%) |
|--------------------------------|-----------------|--|
| 12                             | 3.2             | ≥95  |
| 13-2)                          | 3.2             | ≥95  |
| Ibuprofen                      | 100             | 79.6   |

35 [B] ANALGESIC ACTIVITY :



15

Inflammatory hyperalgesia induced by brewer's yeast  
in rats :

(i) Test Method :

5

Ten male Sprague Dawley rats were used per group.  
0.1 ml of 5% brewer's yeast suspended in 0.5%  
methylcellulose was injected into the right hind paw. The  
pain threshold was determined 3 hours after yeast  
injection, by applying pressure to the foot and reading the  
pressure at which the rat withdrew the foot.

10

The drugs were given orally 2 hours after yeast  
injection. The pain threshold in the treated animals was  
compared with that in the control animals.

15

(ii) Test Results :

| Test compound<br>(Example No.) | Dose<br>(mg/kg) | Relative potency<br>(Control = 1.0) |
|--------------------------------|-----------------|-------------------------------------|
| 1                              | 10              | $\geq 1.4$                          |

20

[C] COX-I and COX-II activity in vitro :

25

(i) Test Method :

a. Preparation of the recombinant cyclooxygenase (COX)

The human cyclooxygenase COX-I and COX-II were  
expressed in transfected Chinese hamster ovary (CHO) cells.  
Monolayer cultures of semi-confluent CHO cells stably  
expressing COX-I and COX-II were washed twice and scraped  
into phosphate buffered saline (PBS). The cells were  
centrifuged at 200 x g for 5 minutes and the cell pellet  
was sonicated in reaction buffer containing 100 mM Tris-HCl

30

35

(pH 7.4), 2  $\mu$ M hematin and 5 mM tryptophan. Broken cells were centrifuged for 5 minutes at 1700 x g at 4°C and the supernatants were used as crude enzymes.

5           Cyclooxygenase activities in the absence or presence of inhibitors were measured by determining the level of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesis from arachidonic acid. Enzymes (1  $\mu$ g for COX-I and/or 3  $\mu$ g for COX-II) in a total volume of 200  $\mu$ l of reaction buffer were incubated in the  
10       absence and presence of various concentrations of inhibitors for 5 minutes at 30°C. The reaction was then started by the addition of arachidonic acid to the final concentration of 10  $\mu$ M. The reaction was terminated by  
15       50  $\mu$ l of HCl (1N) after incubation at 30°C for 5 minutes. PGE<sub>2</sub> was extracted with ethyl acetate, concentrated under a stream of nitrogen and analyzed by a radio immunoassay kit (Amersham) according to the manufacture's instructions.

20           b. Assay for human recombinant COX-I and COX-II activity

          COX activity was assayed as PGE<sub>2</sub> formation using radioimmunoassay to detect the prostaglandin release. The appropriate COX enzyme was incubated in 0.1 M Tris-HCl  
25       buffer (pH 7.3) containing hematin and tryptophan with the addition of arachidonic acid (10  $\mu$ M) for 5 minutes at 37°C. Compounds were pre-incubated with the enzyme for 5 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped  
30       after 5 minutes at 37°C by addition of 20  $\mu$ l of 1N HCl. PGE<sub>2</sub> formation was measured by radioimmunoassay (Amersham).

(ii) Test Results :

| Test compound<br>(Example No.) | Human COX-II<br>IC <sub>50</sub> (μM) | Human COX-I<br>IC <sub>50</sub> (μM) |
|--------------------------------|---------------------------------------|--------------------------------------|
| 13-2)                          | <0.1                                  | ≥60                                  |

5

## [D] Toxicities of Compound (I)

Test on the toxicity by repetitive oral administration of the compound disclosed in Example 13-2) in SD rat was  
10 conducted, and the dead at dose of 32 mg/kg once a day for 14 consecutive days could not be observed.

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present  
15 invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external  
20 (topical) administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances,  
25 stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about  
30 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

5

#### Preparation 1

(1) A mixture of ethyl 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxylate (6.4 g) and sodium methoxide (2.6 g) in N,N-dimethylformamide (60 ml) was stirred at 100°C for 1.5 hours. The resulting mixture was poured into water (200 ml). The resulting precipitates were collected by filtration, washed with water and dried in vacuo to give 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxamide (5.0 g).

15

mp : 112-115°C

IR (Nujol) : 3400, 1680, 1600, 1200 cm<sup>-1</sup>

20

(2) A solution of phosphorous oxychloride (2.78 ml) in N,N-dimethylformamide (60 ml) was stirred at 0°C for 30 minutes. To this solution, 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxamide (5.0 g) was added at one portion. After being stirred for additional 30 minutes, the resulting mixture was poured into a mixture of ice-water (100 ml). The resulting precipitates were collected by filtration, washed with water and dried in vacuo to give 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carbonitrile (3.76 g).

25

mp : 124-125°C

IR (Nujol) : 2250, 1690, 1680, 1510 cm<sup>-1</sup>

30

#### Preparation 2

A mixture of 4-aminoacetophenone (10 g) and sodium nitrite (5.1 g) in acetic acid (55 ml) was stirred at 10°C for 1 hour. To the resulting mixture were added concentrated hydrochloric acid (25 ml) and stannous

35

chloride dihydrate (41 g), and stirred at 0°C for 30 minutes. To the reaction mixture was added 1-[4-(methylthio)phenyl]butane-1,3-dione (15.4 g), and stirred at ambient temperature for 1 hour. The mixture was stirred at 100°C for 3 hours and poured into ice-water. The resulting precipitates were filtered, washed with water, and dried under reduced pressure to give 1-(4-acetylphenyl)-3-methyl-5-[4-(methylthio)phenyl]pyrazole (24.6 g).

- 10 IR (Nujol) : 1680, 1600  $\text{cm}^{-1}$   
NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 2.28 (3H, s), 2.47 (3H, s), 2.57 (3H, s), 6.48 (1H, s), 7.16 (2H, d,  $J=8.5\text{Hz}$ ), 7.25 (2H, d,  $J=8.5\text{Hz}$ ), 7.36 (2H, d,  $J=8.6\text{Hz}$ ), 7.96 (2H, d,  $J=8.6\text{Hz}$ )  
15 MASS (m/z) : 323 (M+1)

### Preparation 3

(1) To a mixture of 1-(4-acetylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (7.85 g) and perchloric acid (70%, 23.6 ml) in the mixture of 1,4-dioxane (40 ml) and methanol (120 ml) was added thallium(III) nitrate trihydrate (14.32 g), and stirred at ambient temperature overnight. The resultant mixture was added to water (140 ml), extracted with toluene, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and toluene (1:5) to give crystals of methyl 4-[5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazol-1-yl]phenylacetate (4.66 g).

- 30 mp : 136-138°C  
IR (Nujol) : 1735, 1605, 1310, 1230  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.08 (3H, s), 3.67 (2H, s), 3.71 (3H, s), 6.84 (1H, s), 7.10-8.00 (8H, m)  
35 MASS (m/z) : 439 (M+1)

(2) The mixture of methyl 4-[5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazol-1-yl]phenylacetate (1.00 g) and 1N-sodium hydroxide (5 ml) in the solution of tetrahydrofuran (5 ml) and methanol (10 ml) was stirred at ambient temperature for 1 hour. The resultant mixture was acidified with hydrochloric acid. The precipitates were filtered and washed with water. The filtrate was recrystallized from ethanol to give crystals of 4-[5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazol-1-yl]phenylacetic acid (0.75 g).

mp : 184-186°C

IR (Nujol) : 1710, 1605, 1305, 1235  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.09 (3H, s), 3.71 (2H, s), 6.85 (1H, s), 7.27 (2H, d,  $J=8.7\text{Hz}$ ), 7.35 (2H, d,  $J=8.7\text{Hz}$ ), 7.44 (2H, d,  $J=8.5\text{Hz}$ ), 7.92 (2H, d,  $J=8.5\text{Hz}$ )

MASS (m/z) : 425 (M+1)

Elemental Analysis Calcd. for  $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_4\text{S}$  :

C 53.77, H 3.56, N 6.60

Found : C 53.44, H 3.38, N 6.36

#### Preparation 4

(1) 4-Chlorophenylhydrazine hydrochloride (4.0 g) was added to a solution of sodium (0.5 g) in ethanol (50 ml), and the mixture was refluxed for 1 hour. To the cooled mixture was added 3-[4-(methylthio)phenyl]acrylonitrile (3.0 g), and the resulting mixture was refluxed overnight. Ethyl acetate and water were added to the reaction mixture. The organic layer was separated, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30 g) eluting with a mixture of toluene and ethyl acetate (9:1) to give 1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]-2-pyrazolin-3-amine (3.4 g).

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 2.44 (3H, s), 2.50 (1H, dd,

21

J=16.4, 5.7Hz), 3.44 (1H, dd, J=16.4, 10.8Hz),  
4.98 (1H, dd, J=10.8, 5.7Hz), 5.84 (2H, br s),  
6.62 (2H, d, J=9.0Hz), 7.02 (2H, d, J=9.0Hz),  
7.02 (4H, s)

5            MASS (m/z) : 318 (M+1)

(2) A mixture of 1-(4-chlorophenyl)-5-[4-(methylthio)-  
phenyl]-2-pyrazoline-3-amine (3.4 g) and manganese(IV)  
oxide (2.7 g) in dichloromethane (500 ml) was stirred at  
10        ambient temperature for 2 hours. The insoluble material  
was filtered and the filtrate was concentrated to dryness.  
The residue was purified by column chromatography on silica  
gel eluting with a mixture of toluene and ethyl acetate  
(4:1) to give 1-(4-chlorophenyl)-5-[4-  
15        (methylthio)phenyl]pyrazole-3-amine (0.82 g).

NMR (DMSO-d<sub>6</sub>, δ) : 2.47 (3H, s), 5.02 (2H, br s),  
5.83 (1H, s), 7.14 (4H, d, J=9Hz), 7.24 (2H, d,  
J=9Hz), 7.38 (2H, d, J=9Hz)

MASS (m/z) : 316 (M+1)

20

#### Preparation 5

(1) 5-[4-(Methylthio)phenyl]-1-phenyl-2-pyrazoline-3-amine  
was prepared from 3-[4-(methylthio)phenyl]-  
acrylonitrile in a similar manner to that of  
25        Preparation 4-(1).

NMR (DMSO-d<sub>6</sub>, δ) : 2.44 (3H, s), 2.48 (1H, dd, J=16,  
6Hz), 3.41 (1H, dd, J=16, 10Hz), 4.93 (1H, dd,  
J=10, 6Hz), 5.73 (2H, br s), 6.49 (1H, t, J=7Hz),  
6.65 (2H, d, J=8Hz), 7.00 (2H, dd, J=7, 8Hz),  
30        7.22 (4H, s)

MASS (m/z) : 284 (M+1)

(2) 5-[4-(Methylthio)phenyl]-1-phenylpyrazole-3-amine was  
prepared from 5-[4-(methylthio)phenyl]-1-phenyl-2-  
35        pyrazoline-3-amine in a similar manner to that of

## Preparation 4-(2).

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.46 (3H, s), 4.95 (2H, br s),  
5.82 (1H, s), 7.09-7.36 (9H, complex m.)

MASS (m/z) : 282 (M+1)

5

Preparation 6

A solution of 5-[4-(methylthio)phenyl]-1-(4-nitrophenyl)pyrazole-3-carboxylic acid (4.8 g) in thionyl chloride (50 ml) was refluxed for 3 hours and concentrated under reduced pressure. A solution of the residue in tetrahydrofuran (50 ml) was added dropwise to a solution of sodium azide (1.1 g) in the mixture of acetone (40 ml) and water (20 ml) at 0°C. The mixture was stirred for 1 hour and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil (5.1 g). A solution of the oil (5.1 g) in N,N-dimethylformamide (50 ml) was stirred at 100° to 110°C for 2 hours and concentrated under reduced pressure. The residue was triturated in a mixture of diisopropyl ether and ethyl ether to give a powder (4.2 g). The mixture of an above powder (4.2 g) and concentrated hydrochloric acid (70 ml) was refluxed for 3 hours and cooled to 0°C. The reaction mixture was adjusted to pH=10 with an aqueous sodium hydroxide and extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (250 g) eluting with a mixture of acetone and dichloromethane (1:10) to give a yellow powder of 5-[4-(methylthio)phenyl]-1-(4-nitrophenyl)pyrazole-3-amine (2.1 g).

mp : 195-196°C

IR (Nujol) : 3400, 3320, 1515, 1330  $\text{cm}^{-1}$

35

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.51 (3H, s), 5.94 (1H, s), 7.15



23

(2H, d, J=8.7Hz), 7.23 (2H, d, J=8.7Hz), 7.38

(2H, d, J=9.2Hz), 8.13 (2H, d, J=9.2Hz)

MASS (m/z) : 327 (M+1)

5 Preparation 7

A solution of 1-(4-cyanophenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxylic acid (2 g) in thionyl chloride (20 ml) was refluxed for 3 hours and concentrated under reduced pressure. A solution of the above residue in tetrahydrofuran (20 ml) was added dropwise to a mixture of sodium azide (0.7 g) and sodium bicarbonate (0.5 g) in a mixture of acetone (20 ml) and water (10 ml) at 0°C. The mixture was stirred for 1 hour and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The solution of the residue in N,N-dimethylformamide (20 ml) was stirred at 100° to 110°C for 1 hour and poured into a mixture of ice and water. The resultant precipitates were collected, washed with water, and dried under reduced pressure. The mixture of the products and concentrated hydrochloric acid (40 ml) was refluxed for 4 hours and adjusted to pH=10 with an aqueous sodium hydroxide. The reaction mixture was extracted with a solution of ethyl acetate and tetrahydrofuran. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (150 g) eluting with a mixture of methanol and chloroform (1:10) to give 4-[5-[4-(methylthio)phenyl]-3-aminopyrazol-1-yl]benzoic acid (0.75 g).

IR (Nujol) : 1605, 1510  $\text{cm}^{-1}$ 

NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.46 (3H, s), 4.95 (2H, br s),  
5.83 (1H, s), 7.04 (2H, d, J=8.3Hz), 7.12 (2H, d,  
J=8.3Hz), 7.21 (2H, d, J=8.3Hz), 7.78 (2H, d,  
J=8.3Hz)

MASS (m/z) : 326 (M+1)

Preparation 8

(1) To a solution of 4-aminoacetophenone (5.42 g) in  
5 acetic acid (42 ml) was added sodium nitrite (2.95 g) at  
room temperature. After stirring for 30 minutes,  
hydrochloric acid (16.8 ml) was added to the mixture at 5°C  
and the resultant mixture was stirred for 20 minutes. Tin  
10 chloride dihydrate (23.28 g) was added by portions for 30  
minutes at 5°C and the resultant mixture was stirred for 20  
minutes at the same temperature. 1-[4-(Methylthio)phenyl]-  
4,4-difluoro-1,3-dioxobutane (7.0 g) was added at 25°C and  
the mixture was stirred for 1 hour at 45°C. To the mixture  
was added water (182 ml) at 20°C. After stirring for 1  
15 hour, the resulting precipitate was collected by filtration  
and washed with water. After drying at 40°C in vacuo  
overnight, to a solution of the crude product in acetone  
(103 ml) was added water (67 ml) dropwise. After stirring  
at 20°C for 1 hour, the resultant precipitate was collected  
20 by filtration, and washed with the mixture of acetone and  
water (3:2, 31 ml) and dried at 40°C in vacuo overnight to  
give 1-(4-acetylphenyl)-3-difluoromethyl-5-[4-(methylthio)-  
phenyl]pyrazole (8.63 g).

25 (2) A mixture of 1-(4-acetylphenyl)-3-difluoromethyl-5-(4-  
methylthiophenyl)pyrazole (8.5 g), tetrabutylammonium  
hydrogensulfate (1.61 g), oxone<sup>®</sup> (30.58 g :  
2KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub>), ethyl acetate (128 ml) and water (85  
ml) was heated under reflux for 2 hours. To the reaction  
30 mixture was added water and ethyl acetate. Organic layer  
was separated and washed with brine and dried over  
magnesium sulfate. After removing magnesium sulfate by  
filtration, the filtrate was concentrated under reduced  
pressure. After dissolving the residue by adding ethyl  
35 acetate at 40°C, the resultant solution was allowed to cool

to room temperature. Then the solution was stirred for an hour with ice-bath cooling. The resulting precipitate was collected by filtration and washed with cold ethyl acetate (13 ml) and dried at 40°C in vacuo overnight to give crude crystals (6.67 g).

The obtained crude crystals (6.50 g) was dissolved in 90% aqueous ethanol (91 ml; ethanol 82 ml and water 9 ml) at 75°C. After stirring for 30 minutes, the filtrate was cooled gradually at 65°C and then seed crystals were added. The temperature of the mixture was cooled to 60°C and was maintained in the range of 55-60°C for 30 minutes. After cooling to 25°C over a period of 1 hour, the temperature was kept in the range of 25-30°C for more than an hour. The resultant precipitate was collected by filtration, washed with ethanol and dried in vacuo at 40°C for more than an hour to give 1-(4-acetylphenyl)-3-difluoromethyl-5-[4-(methylsulfonyl)phenyl]pyrazole (5.85 g).

mp : 145-152°C

IR (Nujol) : 1682, 1602, 1314, 1154  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.63 (3H, s), 3.09 (3H, s), 6.80 (1H t,  $J=54.7\text{Hz}$ ), 6.85 (1H, s), 7.38 (2H, d,  $J=8.7\text{Hz}$ ), 7.44 (2H, d,  $J=8.5\text{Hz}$ ), 7.94 (2H, d,  $J=8.5\text{Hz}$ ), 7.99 (2H, d,  $J=8.7\text{Hz}$ )

MASS (m/z) : 391 (M+H)<sup>+</sup>

#### Example 1

To a stirred solution of 1-(4-acetylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (0.72 g) in methanol (7 ml), sodium borohydride (80 mg) was added portionwise at 15°C. The resulting mixture was stirred for 1 hour at ambient temperature, treated with acetic acid (1 ml) and then concentrated under reduced pressure. To the residue, a mixture of ethyl acetate and water was added, and stirred. The organic layer was separated, washed with an aqueous solution of sodium bicarbonate and subsequently

brine. The solution was dried over magnesium sulfate and concentrated under reduced pressure. The residual oil was crystallized with toluene and filtered to give crystals of  
1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-  
3-(trifluoromethyl)pyrazole (0.54 g).

mp : 138-140°C

IR (Nujol) : 3500, 1605, 1500, 1300 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.33 (3H, d, J=6Hz), 3.26 (3H, s),  
4.77 (1H, m), 5.32 (1H, br d, J=4Hz), 7.33 (2H,  
d, J=8Hz), 7.35 (1H, s), 7.45 (2H, d, J=8Hz),  
7.57 (2H, d, J=8Hz), 7.93 (2H, d, J=8Hz)

MASS (m/z) : 411 (M<sup>+</sup>), 393 (M<sup>+</sup>-18)

#### Example 2

The following compounds described in (1) to (4) were obtained according to a similar manner to that of Example 1.

(1) 1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]-  
3-(trifluoromethyl)pyrazole

mp : 98-99°C

IR (Nujol) : 3450, 1605, 1500, 1270, 1230 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 1.49 (3H, d, J=6Hz), 1.72 (1H, br  
s), 2.48 (3H, s), 4.93 (1H, q, J=6Hz), 6.72 (1H,  
s), 7.12 (2H, d, J=9Hz), 7.18 (2H, d, J=9Hz),  
7.29 (2H, d, J=9Hz), 7.38 (2H, d, J=9Hz)

MASS (m/z) : 379 (M<sup>+</sup>)

(2) 3-Difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 144-146°C

IR (Nujol) : 3400, 1600, 1310, 1150 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 1.50 (3H, d, J=6Hz), 2.05 (1H, br  
s), 3.08 (3H, s), 4.95 (1H, q, J=6Hz), 6.78 (1H,  
t, J=5.5Hz), 6.83 (1H, s), 7.25 (2H, d, J=8Hz),

27

7.41 (2H, d, J=8Hz), 7.44 (2H, d, J=9Hz), 7.89  
(2H, d, J=9Hz)

MASS (m/z) : 393 ( $M^{+1}$ ), 375 ( $M^{+1}-18$ )

- 5 (3) 1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]-  
pyrazole-3-carbonitrile

pale yellow oil

IR (Film) : 3450, 2250, 1605, 1510, 1480  $\text{cm}^{-1}$

10

- (4) 1-[4-(1-Hydroxyethyl)phenyl]-3-methyl-5-[4-  
(methylthio)phenyl]pyrazole

IR (Nujol) : 3250, 1600  $\text{cm}^{-1}$

15 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.32 (3H, d, J=6Hz), 2.25 (3H, s),  
2.46 (3H, s), 4.73 (1H, m), 5.24 (1H, d, J=4Hz),  
6.40 (1H, s), 7.12 (2H, d, J=8Hz), 7.17 (2H, d,  
J=8Hz), 7.21 (2H, d, J=8Hz), 7.35 (2H, d, J=8Hz)

MASS (m/z) : 325 ( $M+1$ )

20 Example 3

To a stirred solution of 4-[5-[4-(methylthio)phenyl]-  
3-(trifluoromethyl)pyrazol-1-yl]benzoic acid (18 g) in  
ether (100 ml), a solution of methyl lithium in ether (1.2N  
solution: 130 ml) was slowly added at ambient temperature.

25 The resulting mixture was refluxed for 1.5 hours and then  
cooled. The reaction mixture was quenched with an aqueous  
saturated solution of ammonium chloride and extracted with  
ethyl acetate several times. The organic layer was washed  
with brine, dried over magnesium sulfate and concentrated  
30 under reduced pressure to give an oil. This oil was  
crystallized with isopropyl ether to give  
1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]-3-  
(trifluoromethyl)pyrazole (8.5 g).

mp : 138-140°C

35 IR (Nujol) : 1690, 1600, 1270, 1240  $\text{cm}^{-1}$

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.49 (3H, s), 2.62 (3H, s), 6.75 (1H, s), 7.12 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz), 7.43 (2H, d, J=9Hz), 7.96 (2H, d, J=9Hz)

5 The following compound was obtained as a by-product.

1-[4-(1-Hydroxy-1-methylethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole

10 Yellow oil

IR (Nujol) : 3400, 1600, 1500, 1470, 1440, 1230 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.57 (3H, s), 1.58 (3H, s), 2.48 (3H, s), 6.72 (1H, s), 7.13 (2H, d, J=9Hz), 7.18 (2H, d, J=9Hz), 7.24 (2H, d, J=9Hz), 7.49 (2H, d, J=9Hz)

15 MASS (m/z) : 393 (M<sup>+</sup>)

#### Example 4

20 A mixture of 1-[4-(1-hydroxy-1-methylethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole (1.1 g) and m-chloroperbenzoic acid (0.55 g) in dichloromethane (30 ml) was stirred at 5°C for 30 minutes. The resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate and subsequently brine. The solution  
25 was dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel and eluted with dichloromethane. The fractions containing object compound were combined and concentrated under reduced pressure to  
30 give an amorphous powder. This powder was washed with n-hexane to give 1-[4-(1-hydroxy-1-methylethyl)phenyl]-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole (0.54 g).

IR (Neat) : 3400, 1600, 1500, 1470, 1440 cm<sup>-1</sup>

35 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.59 (6H, s), 2.76 (3H, s), 6.81

(1H, s), 7.26 (2H, d, J=9Hz), 7.40 (2H, d, J=8Hz), 7.51 (2H, d, J=9Hz), 7.62 (2H, d, J=8Hz)  
MASS (m/z) : 409 ( $M^{+1}$ ), 391 ( $M^{+1}-18$ )

### 5 Example 5

A mixture of 1-[4-(1-hydroxy-1-methylethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole (1.5 g) and m-chloroperbenzoic acid (1.45 g) in dichloromethane (35 ml) was stirred at ambient temperature for one hour. The  
10 resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate and subsequently brine. The organic solution was dried over magnesium sulfate and concentrated under reduced pressure. The residual oil was subjected to column chromatography on silica gel and eluted  
15 with a mixture of toluene and ethyl acetate. The fractions containing object compound were combined and concentrated under reduced pressure to give a white powder. This powder was crystallized with a mixture of ethanol and water to give 1-[4-(1-hydroxy-1-methylethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (0.52  
20 g).

mp : 147-148°C

IR (Nujol) : 3550, 1610, 1500, 1410  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.60 (6H, s), 3.09 (3H, s), 6.85

25 (1H, s), 7.26 (2H, d, J=9Hz), 7.45 (2H, d, J=8Hz), 7.53 (2H, d, J=9Hz), 7.91 (2H, d, J=8Hz)

MASS (m/z) : 425 ( $M^{+1}$ )

### Example 6

30 To a solution of 1-(4-acetylphenyl)-3-methyl-5-[4-(methylthio)phenyl]pyrazole (2.0 g) in tetrahydrofuran (50 ml) was added a 1N-solution (31 ml) of methylmagnesium bromide in tetrahydrofuran, and stirred for 5 hours at 0°C. To the resultant mixture was added water, extracted with  
35 ethyl acetate, washed with brine, dried over magnesium

sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate (5:1) to give 1-[4-(1-hydroxy-1-methylethyl)phenyl]-3-methyl-5-  
5 [4-(methylthio)phenyl]pyrazole (0.64 g).

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.42 (6H, s), 2.25 (3H, s), 2.46 (3H, s), 5.09 (1H, s), 6.40 (1H, s), 7.13 (2H, d, J=8.7Hz), 7.15 (2H, d, J=8.6Hz), 7.21 (2H, d, J=8.7Hz), 7.46 (2H, d, J=8.6Hz)

10 MASS (m/z) : 339 (M+1)

#### Example 7

The following compounds described in (1) to (4) were obtained according to a similar manner to that of Example  
15 4.

(1) 1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfinyl)-phenyl]-3-(trifluoromethyl)pyrazole  
amorphous powder

20 IR (Neat) : 1610, 1500, 1470, 1400  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.50 (3H, d, J=6Hz), 2.75 (3H, s), 4.95 (1H, q, J=6Hz), 6.82 (1H, s), 7.28 (2H, d, J=8Hz), 7.40 (2H, d, J=9Hz), 7.40 (2H, d, J=8Hz), 7.62 (2H, d, J=9Hz)

25 MASS (m/z) : 377 ( $M^{+1}-18$ )

(2) 1-[4-(1-Hydroxyethyl)phenyl]-3-methyl-5-[4-(methylsulfinyl)phenyl]pyrazole

IR ( $\text{CHCl}_3$ ) : 3350, 1610  $\text{cm}^{-1}$

30 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.32 (3H, d, J=6.4Hz), 2.28 (3H, s), 2.76 (3H, s), 4.74 (1H, qd, J=6.4, 4.4Hz), 5.24 (1H, d, J=4.4Hz), 6.53 (1H, s), 7.18 (2H, d, J=8.4Hz), 7.36 (2H, d, J=8.4Hz), 7.40 (2H, d, J=8.4Hz), 7.65 (2H, d, J=8.4Hz)

35 MASS (m/z) : 341 (M+1)



(3) 1-[4-(1-Hydroxy-1-methylethyl)phenyl]-3-methyl-5-[4-(methylsulfinyl)phenyl]pyrazole

mp : 121-122°C

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.42 (6H, s), 2.28 (3H, s), 2.76 (3H, s), 5.10 (1H, s), 6.53 (1H, s), 7.16 (2H, d, J=8.5Hz), 7.40 (2H, d, J=8.3Hz), 7.48 (2H, d, J=8.5Hz), 7.65 (2H, d, J=8.3Hz)

MASS (m/z) : 355 (M+1)

10 (4) 1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfinyl)-phenyl]pyrazole-3-carbonitrile

amorphous powder

IR (Neat) : 3400, 2280, 1600, 1510 cm<sup>-1</sup>

15 NMR (CDCl<sub>3</sub>, δ) : 1.51 (3H, d, J=7Hz), 2.15 (1H, d, J=4Hz), 2.75 (3H, s), 4.95 (1H, dd, J=7, 4Hz), 6.93 (1H, s), 7.25 (2H, d, J=4Hz), 7.37 (2H, d, J=9Hz), 7.42 (2H, d, J=9Hz), 7.63 (2H, d, J=9Hz)

MASS (m/z) : 352 (M<sup>+</sup>), 334 (M<sup>+</sup>-18)

20

#### Example 8

1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile was prepared from the 1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]pyrazole-3-carbonitrile in a similar manner to that of Example 5.

25

mp : 112-113°C

IR (Nujol) : 3350, 2250, 1510, 1310 cm<sup>-1</sup>

30 NMR (CDCl<sub>3</sub>, δ) : 1.52 (3H, d, J=6Hz), 1.97 (1H, br s), 3.08 (3H, s), 4.97 (1H, q, J=6Hz), 6.97 (1H, s), 7.25 (2H, d, J=9Hz), 7.42 (2H, d, J=8Hz), 7.44 (2H, d, J=9Hz), 7.92 (2H, d, J=8Hz)

MASS (m/z) : 368 (M<sup>+</sup>), 350 (M<sup>+</sup>-18)

#### Example 9

35

To the mixture of 4-[5-[4-(methylsulfonyl)phenyl]-3-

(trifluoromethyl)pyrazol-1-yl]phenylacetic acid (1.00 g) in tetrahydrofuran (10 ml) was added dropwise the 1M solution of borane in tetrahydrofuran (5 ml), and stirred at ambient temperature overnight. The several drops of acetic acid was added to the resultant mixture. The mixture was concentrated under reduced pressure and water was added to the resultant. The mixture was extracted with ethyl acetate, washed with brine, dried, concentrated under reduced pressure and recrystallized from a mixture of ethanol and water to give white crystals of 1-[4-(2-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (0.70 g).

mp : 132-134°C

IR (Nujol) : 3505, 1605, 1300, 1280, 1235  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.46 (1H, br s), 2.92 (2H, t,  $J=6.5\text{Hz}$ ), 3.89 (2H, br t,  $J=6.5\text{Hz}$ ), 6.85 (1H, s), 7.23 (2H, d,  $J=8.7\text{Hz}$ ), 7.29 (2H, d,  $J=8.7\text{Hz}$ ), 7.44 (2H, d,  $J=8.4\text{Hz}$ ), 7.91 (2H, d,  $J=8.4\text{Hz}$ )

MASS (m/z) : 411 (M+1)

#### Example 10

A solution of sodium nitrite (0.22 g) in water (5 ml) was added to an ice cooled mixture of 1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]pyrazole-3-amine (0.82 g) and concentrated hydrochloric acid (3 ml). The mixture was stirred at 0°C for 30 minutes and added portionwise to a mixture of cuprous chloride (0.51 g) and concentrated hydrochloric acid (5 ml) at ambient temperature. The mixture was refluxed for 1 hour, and extracted with dichloromethane. The extract was washed with water, dried, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel eluting with toluene to give crystals of 3-chloro-1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]pyrazole (0.38 g).

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 2.47 (3H, s), 6.80 (1H, s), 7.17

(2H, d, J=8.7Hz), 7.26 (2H, d, J=8.7Hz), 7.32

(2H, d, J=8.8Hz), 7.51 (2H, d, J=8.8Hz)

MASS (m/z) : 335 (M+1)

5 Example 11

The following compounds described in (1) to (3) were obtained according to a similar manner to that of Example 10.

10 (1) 3-Chloro-5-[4-(methylthio)phenyl]-1-phenylpyrazole  
NMR (DMSO-d<sub>6</sub>, δ) : 2.46 (3H, s), 6.78 (1H, s), 7.15  
(2H, d, J=8.7Hz), 7.23 (2H, d, J=8.7Hz), 7.24-  
7.31 (2H, m), 7.41-7.46 (3H, m)  
MASS (m/z) : 301 (M+1)

15

(2) 3-Chloro-1-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-  
pyrazole  
NMR (CDCl<sub>3</sub>, δ) : 2.48 (3H, s), 6.40 (1H, s), 7.03  
(2H, t, J=9.1Hz), 7.09 (2H, d, J=8.7Hz), 7.17  
20 (2H, d, J=8.7Hz), 7.26 (2H, dd, J=9.1, 4.8Hz)  
MASS (m/z) : 319 (M+1)

(3) 3-Chloro-5-[4-(methylthio)phenyl]-1-(4-nitrophenyl)-  
pyrazole

25

mp : 195-197°C

IR (Nujol) : 1525, 1375, 1345 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 2.50 (3H, s), 6.46 (1H, s), 7.13  
(2H, d, J=8.5Hz), 7.22 (2H, d, J=8.5Hz), 7.47  
(2H, d, J=9.0Hz), 8.20 (2H, d, J=9.0Hz)

30

MASS (m/z) : 346 (M+H)<sup>+</sup>

Example 12

A solution of m-chloroperbenzoic acid (0.49 g) in  
dichloromethane (10 ml) was added dropwise to a solution of  
35 3-chloro-1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]-

pyrazole (0.38 g) and stirred at ambient temperature for 1 hour. The mixture was washed with an aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate (50:1) to give crystals of 3-chloro-1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole.

mp : 177-178°C

10 IR (Nujol) : 1310, 1140  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 3.25 (3H, s), 6.99 (1H, s), 7.35 (2H, d,  $J=8.8\text{Hz}$ ), 7.53 (4H, d,  $J=8.7\text{Hz}$ ), 7.94 (2H, d,  $J=8.5\text{Hz}$ )

MASS (m/z) : 367 (M+1)

15 Elemental Analysis Calcd. for  $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_2\text{S}$  :

C 52.33, H 3.29, N 7.63

Found : C 52.73, H 3.44, N 7.70

### Example 13

20 The following compounds described in (1) to (3) were obtained according to a similar manner to that of Example 12.

(1) 3-Chloro-5-[4-(methylsulfonyl)phenyl]-1-phenylpyrazole

25 mp : 187-188°C

IR (Nujol) : 1600, 1310, 1150  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 3.23 (3H, s), 6.97 (1H, s), 7.29-7.35 (2H, m), 7.40-7.47 (3H, m), 7.50 (2H, d,  $J=8.5\text{Hz}$ ), 7.90 (2H, d,  $J=8.5\text{Hz}$ )

30 MASS (m/z) : 333 (M+1)

Elemental Analysis Calcd. for  $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_2\text{S}$  :

C 57.74, H 3.94, N 8.42

Found : C 57.81, H 3.90, N 8.05

35 (2) 3-Chloro-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)-

phenyl]pyrazole

mp : 173°C

IR (Nujol) : 1600, 1310, 1150  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 3.24 (3H, s), 6.97 (1H, s), 7.30

5 (2H, t,  $J=9.2\text{Hz}$ ), 7.40 (2H, dd,  $J=9.2$ ,  $5.1\text{Hz}$ ),

7.51 (2H, d,  $J=8.6\text{Hz}$ ), 7.92 (2H, d,  $J=8.6\text{Hz}$ )

MASS (m/z) : 351 (M+1)

Elemental Analysis Calcd. for  $\text{C}_{16}\text{H}_{12}\text{ClFN}_2\text{O}_2\text{S}$  :

C 54.78, H 3.45, N 7.99

10 Found : C 54.63, H 3.35, N 7.88

(3) 3-Chloro-5-[4-(methylsulfonyl)phenyl]-1-(4-nitrophenyl)pyrazole

mp : 189-191°C

15 IR (Nujol) : 1525, 1345, 1315, 1155  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.11 (3H, s), 6.59 (1H, s), 7.45

(2H, d,  $J=9.0\text{Hz}$ ), 7.45 (2H, d,  $J=8.4\text{Hz}$ ), 7.97

(2H, d,  $J=8.4\text{Hz}$ ), 8.24 (2H, d,  $J=9.0\text{Hz}$ )

MASS (m/z) : 378 (M+1)

20 Elemental Analysis Calcd. for  $\text{C}_{16}\text{H}_{12}\text{ClN}_3\text{O}_4\text{S}$  :

C 50.93, H 3.18, N 11.14

Found : C 50.63, H 3.30, N 11.18

#### Example 14

25 A solution of m-chloroperbenzoic acid (0.68 g) in dichloromethane (5 ml) was added dropwise to an ice-salt cooled solution of 3-chloro-1-(4-fluorophenyl)-5-[4-(methylthio)phenyl]pyrazole (1.0 g), and stirred at 0°C for 40 minutes. The mixture was washed with an aqueous

30 solution of sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of ac tone and dichloromethane (1:10) to give amorphous powder of 3-chloro-1-(4-

35 fluorophenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole (0.25

g).

IR (Nujol) : 1510, 1050  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 2.75 (3H, s), 6.50 (1H, s), 7.05

(2H, t,  $J=9.0\text{Hz}$ ), 7.25 (2H, dd,  $J=9.0, 4.8\text{Hz}$ ),

5 7.36 (2H, d,  $J=8.6\text{Hz}$ ), 7.62 (2H, d,  $J=8.6\text{Hz}$ )

MASS (m/z) : 335 (M+1)

#### Example 15

A solution of sodium nitrite (0.5 g) in water (5 ml)  
10 was added to the mixture of 4-[3-amino-5-[4-(methylthio)  
phenyl]pyrazol-1-yl]benzoic acid (1.5 g) in a solution of  
20% hydrochloric acid (30 ml) at 0°C. The reaction mixture  
was stirred at 0°C for 30 minutes and added portionwise to  
a mixture of cuprous chloride (1.0 g) and concentrated  
15 hydrochloric acid (10 ml). The mixture was refluxed for 2  
hours and extracted with a mixture of ethyl acetate and  
tetrahydrofuran. The extract was washed with water, dried  
over magnesium sulfate, and concentrated under reduced  
pressure. A mixture of the residue in thionyl chloride (15  
20 ml) was refluxed for 2 hours, and then concentrated under  
reduced pressure. The solution of the residue in  
tetrahydrofuran was added dropwise to a stirred mixture of  
ammonium hydroxide (28%, 5 ml) and tetrahydrofuran (20 ml)  
at 0°C, and the resulting mixture was stirred at the same  
25 temperature for one hour. The mixture was acidified with  
hydrochloric acid and extracted with ethyl acetate. The  
extract was washed with brine, dried over magnesium  
sulfate, and concentrated under reduced pressure.  
A solution of phosphorus oxychloride (2.0 g) in  
30 N,N-dimethylformamide (10 ml) was stirred at 5°C for 30  
minutes. To the solution was added a solution of the above  
residue in N,N-dimethylformamide, and stirred at 5°C for 2  
hours. The reaction mixture was poured into ice-water and  
the resultant precipitate were collected. The precipitates  
35 were washed with water and dried. To the solution of the

precipitate in dichloromethane (50 ml) was added dropwise a solution of m-chloroperbenzoic acid (1.7 g) in dichloromethane (40 ml) at 5°C and stirred at ambient temperature for 1 hour. The resulting mixture was washed with an aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and n-hexane (1:3) to give 3-chloro-1-(4-cyanophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (155 mg).

mp : 160-165°C (decomp.)

IR (Nujol) : 2240, 1605, 1510, 1310, 1150  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 3.09 (3H, s), 6.56 (1H, s), 7.39

(2H, d,  $J=8.8\text{Hz}$ ), 7.43 (2H, d,  $J=8.8\text{Hz}$ ), 7.66

(2H, d,  $J=8.8\text{Hz}$ ), 7.96 (2H, d,  $J=8.8\text{Hz}$ )

MASS (m/z) : 358 (M+1)

#### Example 16

To a mixture of (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (1.99 g) in dichloromethane (30 ml) was added borane-dimethyl sulfide complex (14.0 ml) under nitrogen atmosphere at room temperature and the resultant mixture was stirred for 1 hour. A solution of 1-(4-acetylphenyl)-3-difluoromethyl-5-[4-(methylthio)phenyl]pyrazole (20.69 g) in dichloromethane (120 ml) was added dropwise to the mixture at -20°C. After standing overnight at 5°C, to the reaction mixture was added methanol (38.5 ml) and the resultant solution was concentrated under reduced pressure. Adding methanol (38.5 ml) followed by evaporation was repeated 3 times. And adding toluene (38.5 ml) followed by evaporation was also repeated 3 times. The resultant product was purified with column chromatography over silica gel eluting with dichloromethane followed with 10% ethyl acetate in dichloromethane and recrystallized from a mixture of ethanol and water (2:1) to give (+)-3-

difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]pyrazole (16.4 g).

mp : 59.67°C

IR (Nujol) : 3700-3100, 1600, 1342, 1162  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.50 (3H, d,  $J=6.5\text{Hz}$ ), 1.91 (1H, d,  $J=3.7\text{Hz}$ ), 2.48 (3H, s), 4.93 (1H, dq,  $J=6.5$ ,  $3.7\text{Hz}$ ), 6.70 (1H, s), 6.76 (1H, dd,  $J=55.0\text{Hz}$ ), 7.15 (2H, d,  $J=8.0\text{Hz}$ ), 7.17 (2H, d,  $J=8.0\text{Hz}$ ), 7.28 (2H, d,  $J=8.5\text{Hz}$ ), 7.38 (2H, d,  $J=8.5\text{Hz}$ )

10 MASS (m/z) : 361 ( $\text{M}+\text{H}$ )<sup>+</sup>

$[\alpha]_{\text{D}}^{27.9} = 13.38$  ( $c=1.050$ ,  $\text{CH}_3\text{OH}$ )

#### Example 17

To a mixture of (+)-3-difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]pyrazole (14.4 g), sodium bicarbonate (14.4 g), dichloromethane (100 ml) and water (160 ml) was added m-chloroperbenzoic acid (80%, 15.18 g) over a period of 15 minutes with vigorously stirring at 0°C. The resultant mixture was stirred for 1.5 hours at the same temperature. After adding water, the organic layer was separated washed with aqueous solution of sodium disulfite and sodium bicarbonate and with brine, and dried over magnesium sulfate. The resultant solution was concentrated under reduced pressure and recrystallized from ethanol (100 ml) to give (+)-3-difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole (13.43 g).

mp : 149-150°C

IR (Nujol) : 3503, 1610, 1323, 1143  $\text{cm}^{-1}$

30 NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.34 (3H, d,  $J=6.4\text{Hz}$ ), 3.26 (3H, s), 4.77 (1H, qd,  $J=6.4$ ,  $4.4\text{Hz}$ ), 5.30 (1H, d,  $J=4.4\text{Hz}$ ), 7.11 (1H, s), 7.15 (1H, d,  $J=54.3\text{Hz}$ ), 7.29 (2H, d,  $J=8.4\text{Hz}$ ), 7.43 (2H, d,  $J=8.4\text{Hz}$ ), 7.54 (2H, d,  $J=8.5\text{Hz}$ ), 7.92 (2H, d,  $J=8.5\text{Hz}$ )

35 MASS (m/z) : 393 ( $\text{M}+\text{H}$ )<sup>+</sup>



$$[\alpha]_D^{28.7} = 11.73 \text{ (c=1.570, CH}_3\text{OH)}$$

#### Example 18

The following compounds described in (1) to (3) were  
5 obtained according to a similar manner to that of Example  
16.

(1) (-)-3-Difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-  
[4-(methylthio)phenyl]pyrazole

10 mp : 60-68°C

$$[\alpha]_D^{27.6} = -12.95 \text{ (c=1.004, CH}_3\text{OH)}$$

(2) (+)-1-[4-(1-Hydroxyethyl)phenyl]-5-[4-  
(methylthio)phenyl]-3-(trifluoromethyl)pyrazole

15 NMR (CDCl<sub>3</sub>, δ) : 1.49 (3H, d, J=6.5Hz), 2.48 (3H, s),  
4.93 (1H, q, J=6.5Hz), 6.72 (1H, s), 7.12 (2H, d,  
J=8.8Hz), 7.17 (2H, d, J=8.8Hz), 7.29 (2H, d,  
J=8.6Hz), 7.38 (2H, d, J=8.6Hz)

$$[\alpha]_D^{25} = 11.74 \text{ (c=2.535, CH}_3\text{OH)}$$

20 (3) (-)-1-[4-(1-Hydroxyethyl)phenyl]-5-[4-  
(methylthio)phenyl]-3-(trifluoromethyl)pyrazole

25 NMR (CDCl<sub>3</sub>, δ) : 1.49 (3H, d, J=6.4Hz), 2.48 (3H, s),  
4.93 (1H, q, J=6.4Hz), 6.72 (2H, s), 7.12 (2H, d,  
J=8.8Hz), 7.17 (2H, d, J=8.8Hz), 7.29 (2H, d,  
J=8.6Hz), 7.38 (2H, d, J=8.6Hz)

$$[\alpha]_D^{26} = -7.22 \text{ (c=1.89, CH}_3\text{OH)}$$

#### Example 19

30 The following compounds described in (1) to (3) were  
prepared according to a similar manner to that of Example  
17.

(1) (-)-3-Difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-  
35 [4-(methylsulfonyl)phenyl]pyrazole

40

mp : 150-151°C

IR (Nujol) : 3510, 1610, 1325, 1148 cm<sup>-1</sup>

NMR (CDCl<sub>3</sub>, δ) : 1.51 (1H, d, J=6.5Hz), 1.97 (1H, d,  
J=3.6Hz), 3.08 (3H, s), 4.96 (1H, qd, J=6.4,  
3.6Hz), 6.78 (1H, dd, J=54.8Hz), 6.83 (1H, s),  
7.25 (1H, d, J=7.4Hz), 7.41 (1H, d, J=7.4Hz),  
7.44 (2H, d, J=8.5Hz), 7.90 (2H, d, J=8.5Hz)

MASS (m/z) : 393 (M+H)<sup>+</sup>

[α]<sub>D</sub><sup>28.7</sup> = -12.24 (c=1.103, CH<sub>3</sub>OH)

(2) (+)-1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

mp : 120-121°C

NMR (CDCl<sub>3</sub>, δ) : 1.50 (3H, d, J=6.5Hz), 1.95 (1H, d,  
J=3.7Hz), 3.08 (3H, s), 4.96 (1H, qd, J=6.5,  
3.7Hz), 6.85 (1H, s), 7.27 (2H, d, J=8.45Hz),  
7.42 (2H, d, J=8.5Hz), 7.44 (2H, d, J=8.3Hz),  
7.91 (2H, d, J=8.3Hz)

MASS (m/z) : 411 (M+H)<sup>+</sup>

[α]<sub>D</sub><sup>28</sup> = 8.5 (c=1.000, EtOH)

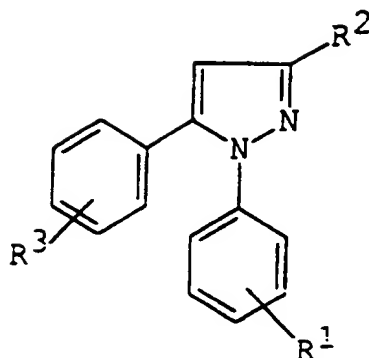
(3) (-)-1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

mp : 124-129°C

41

## C L A I M S

1. A compound of the formula :



[I]

wherein R<sup>1</sup> is hydroxyethyl, 1-hydroxy-1-methylethyl,  
hydrogen, halogen, nitro, or cyano,  
R<sup>2</sup> is chloro, cyano, or lower alkyl optionally  
substituted with halogen, and  
R<sup>3</sup> is lower alkylthio, lower alkylsulfinyl, or  
lower alkylsulfonyl,  
provided that when R<sup>1</sup> is hydrogen, halogen, nitro, or  
cyano,  
then R<sup>2</sup> is chloro,  
and a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1,  
wherein R<sup>1</sup> is hydroxyethyl or 1-hydroxy-1-methylethyl,  
R<sup>2</sup> is cyano or lower alkyl optionally  
substituted with halogen, and  
R<sup>3</sup> is lower alkylthio, lower alkylsulfinyl or  
lower alkylsulfonyl.

3. The compound according to claim 1,

wherein  $R^1$  is hydrogen, halogen, nitro or cyano,

$R^2$  is chloro, and

$R^3$  is lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl.

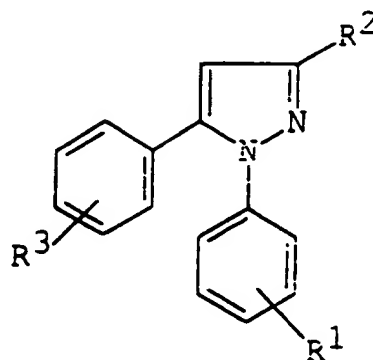
5

4. The compound according to claim 3,  
wherein  $R^1$  is hydrogen or halogen.

5. A process for preparing a compound of the formula :

10

15



[I]

20

wherein  $R^1$  is hydroxyethyl, 1-hydroxy-1-methylethyl,  
hydrogen, halogen, nitro, or cyano,

25

$R^2$  is chloro, cyano, or lower alkyl optionally  
substituted with halogen, and

$R^3$  is lower alkylthio, lower alkylsulfinyl, or  
lower alkylsulfonyl,

provided that when  $R^1$  is hydrogen, halogen, nitro, or  
cyano,

30

then  $R^2$  is chloro,

or a salt thereof,

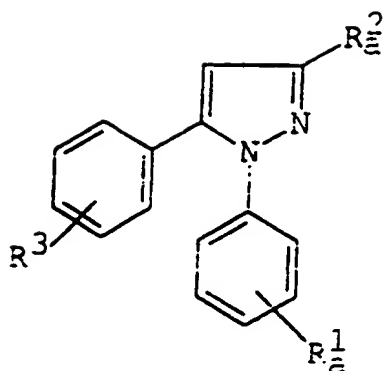
which comprises,

35

a) reducing a compound of the formula :

43

5



[II]

10

15

wherein  $R^3$  is as defined above,

$R_a^1$  is acetyl, and

$R_a^2$  is cyano or lower alkyl optionally

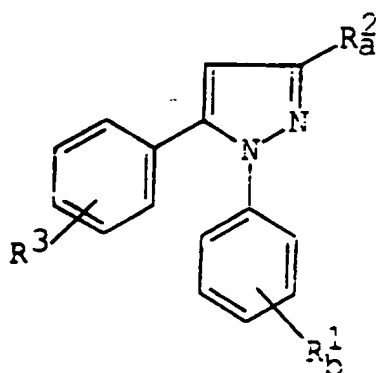
substituted with halogen,

or a salt thereof,

20

to give a compound of the formula :

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[Ia]

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wherein  $R_a^2$  and  $R^3$  are each as defined above, and

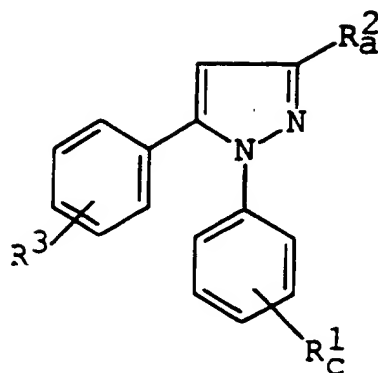
35

$R_5^1$  is 1-hydroxyethyl,

44

or a salt thereof,

b) subjecting a compound of the formula :

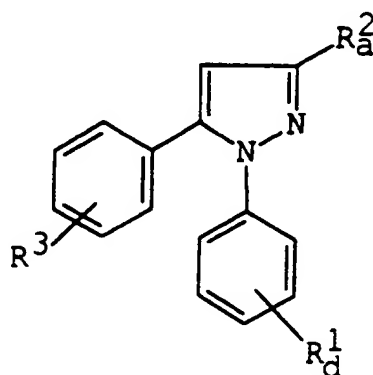


[III]

wherein R<sup>2</sup><sub>a</sub> and R<sup>3</sup> are each as defined above and  
R<sup>1</sup><sub>C</sub> is carboxy,

or its reactive derivative at the carboxy group,  
or a salt thereof,

to alkylation to give a compound of the formula :

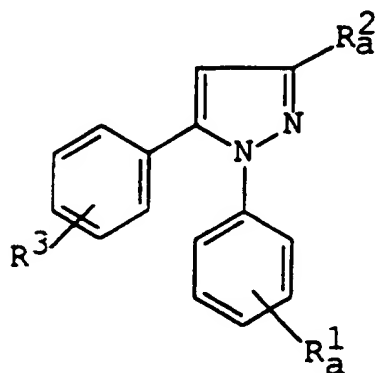


[Ib]

45

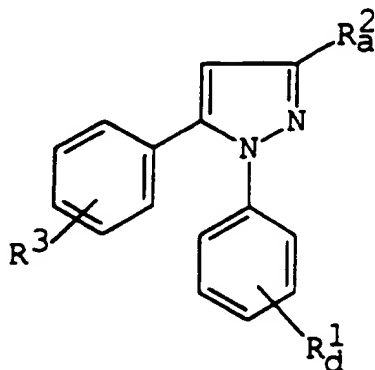
wherein  $R_a^2$  and  $R^3$  are each as defined above and  
 $R_d^1$  is 1-hydroxy-1-methylethyl,  
or a salt thereof

5 c) subjecting a compound of the formula :



[II]

20 wherein  $R_a^1$ ,  $R_a^2$  and  $R^3$  are each as defined above,  
or a salt thereof,  
to alkylation at the acetyl group to give a compound  
of the formula :



[Ic]

d)

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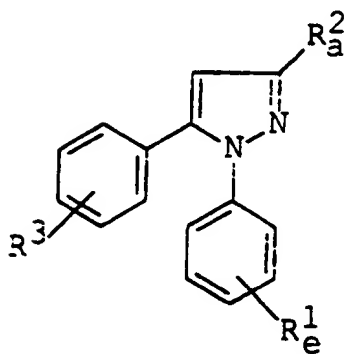
47

wherein  $R^1$  and  $R^2$  are each as defined above and  
 $R^3$  is lower alkylsulfinyl or lower  
 alkylsulfonyl,  
 or a salt thereof

5

e) reducing a compound of the formula :

10



[IV]

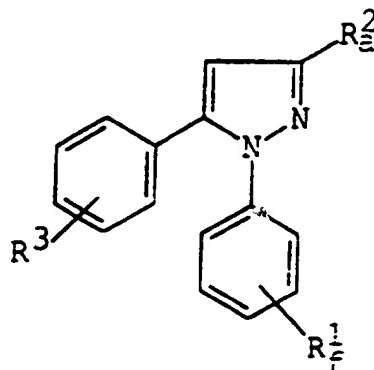
15

20

wherein  $R^2$  and  $R^3$  are each as defined above and  
 $R^1_e$  is carboxymethyl,  
 or its reactive derivative at the carboxy group,  
 or a salt thereof,  
 to give a compound of the formula :

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30



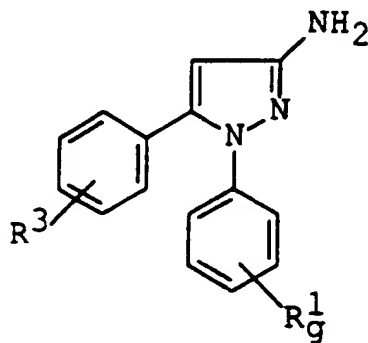
[If]

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48

wherein  $R_a^2$  and  $R^3$  are each as defined above and  
 $R_f^1$  is 2-hydroxyethyl,  
or a salt thereof, or

5 f) subjecting a compound of the formula :

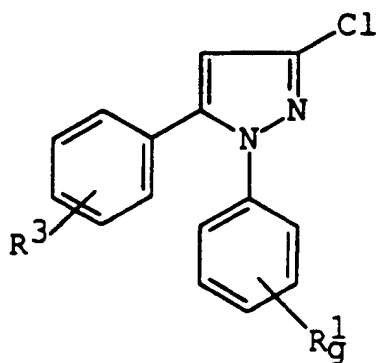


[V]

wherein  $R^3$  is as defined above and

$R_g^1$  is hydrogen, halogen, nitro or cyano,  
or a salt thereof,

to chlorination to give a compound of the formula :



[Ig]

wherein  $R_g^1$  and  $R^3$  are each as defined above,  
or a salt thereof.

- 5           6. A pharmaceutical composition comprising the compound  
of claim 1, as an active ingredient, in association  
with a pharmaceutically non-toxic carrier or  
excipient.
- 10          7. A compound of claim 1 for use as a medicament.
8. COX-II inhibiting agent comprising the compound of  
claim 1.
- 15          9. A method for the treatment and/or prevention of  
inflammatory conditions, various pains, collagen  
diseases, autoimmune diseases, various immunity  
diseases, analgesic, thrombosis, cancer or  
neurodegenerative diseases which comprises administering  
an effective amount of the compound of claim 1 to  
20 human beings or animals.
- 25          10. Use of the compound of claim 1 for the manufacture of  
a medicament for treatment and/or prevention of  
inflammatory conditions, various pains, collagen  
diseases, autoimmune diseases, various immunity  
diseases, analgesic, thrombosis, cancer or  
neurodegenerative diseases in human beings or animals.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 96/02919

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D231/12 C07D231/14 A61K31/415 C07D231/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

3 December 1996

Date of mailing of the international search report

17 -01- 1997

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Authorized officer

Herz, C

# INTERNATIONAL SEARCH REPORT

Intern: al Application No

PCT/JP 95/02919

C/(Continuation) D CUMENTS C NSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages                       | Relevant to claim No. |
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| A        | WO,A,95 15318 (G. D. SEARLE & CO.) 8 June 1995<br>cited in the application<br>see claims 1,9,17<br>----- | 1-10                  |

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information on patent family members

International Application No.

PCT/JP 96/02919

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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information on patent family members

International Application No

**PCT/JP 96/02919**

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